Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 2-6 and 8 are pending in the application, with claims 2 and 8 being the independent claims. Claims 1, 7 and 9-29 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. The foregoing amendments are believed to introduce no new matter, and their entry is respectfully requested. Support for the amendments in claims 2 and 8 can be found on page 15 of the specification.

Applicants confirm the election of Group I (claims 1-8, drawn to polypeptides and a composition comprising polypeptides, classified in class 530, subclass 351+) and of SEQ ID NO. 1 as a species. As the Examiner stated on page 4 of the Restriction Requirement (Paper No. 9), "upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species that is elected consonant with this requirement, and a listing of all claims readable thereupon, including any claims subsequently added."

Applicants respectfully disagree with Examiner's decision to withdraw part (d) of claim 8 from consideration, as it is improper to withdraw a part of a claim. Moreover, part (d) of claim 8 is drawn to N- or C- derivatives of SEQ ID NO:1, and it uses the same language as part (d) in claim 2, which the Examiner agreed to examine. N- and C-derivatives were not listed as a separate species to be elected in the previous Restriction

Requirement. Applicants respectfully contend that part (d) of claim 8 is drawn to an elected invention and, therefore, Applicants respectfully request that it be examined.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Objection to the Specification

In the Office Action at page 2, the Examiner objected to the Figures. The Figures will be amended in accordance with Form PTO 948 when the claims are allowed. Per Examiner's request, a copy of Form PTO 948 is enclosed with this reply.

In the Office Action at pages 2-3, the Examiner objected to the Abstract for lack of narrative form. By the foregoing amendment, Applicants corrected the Abstract appropriately.

In the Office action at page 3, the Examiner stated that the Application is not in compliance with the sequence rules 37 C.F.R. §§ 1.821-1.825. Applicants respectfully disagree with the objection. 37 C.F.R. § 1.821 requires that sequences of at least 4 amino acids in length, ***specifically defined***, be given a sequence listing number and be identified by a SEQ ID NO. Specifically defined means those amino acids other than "Xaa" defined in accordance with the World Intellectual Property Organization, i.e. the sequence spelled out in the form XaaXaaXaaXaa *et cetera*. Applicants have spelled out the sequences and given them SEQ ID NOs. on pages 21 and 22. In addition, Applicants refer to these sequences by a name, such as [desaminoAla^{1}]hPTH(1-34), the way "albumin" would designate a gene of a particular sequence. Just as "albumin" would not require a SEQ ID

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NO. designation after it, so does [desaminoAla^{1}]hPTH(1-34) not require such a designation. Therefore, Applicants respectfully request that the objection to the specification be withdrawn.

II. Rejection under 35 U.S.C. § 101

In the Office Action at page 3, the Examiner rejected claims 1,2 and 5-8 as directed to non-statutory matter because the claims read on a product of nature. By the foregoing amendments, claims 2 and 8 were amended in accordance with the Examiner's suggestion, and claims 1 and 7 have been cancelled, thus rendering moot the portion of this rejection that may have applied to these claims.

III. Rejection under 35 U.S.C. § 112, First Paragraph

In the Office Action at page 4, the Examiner rejected claims 1, 2 and 5-8 under 35 U.S.C. § 112 for not reasonably providing enablement for all variants of SEQ ID NO: 1. By the foregoing amendments, claims 1 and 7 have been cancelled, thus rendering moot the portion of this rejection that may have applied to these claims. Applicants respectfully traverse the rejection as it may apply to the remaining claims.

If the Examiner's argument was intended to apply to the currently pending claims, Applicants respectfully disagree. Applicants limit the possible amino acid composition of the polypeptides by using the term "consisting essentially of" rather than "comprising." In addition, Applicants provide specific amino acid substitutions at a specific position in these peptides. Applicants also provide data in the application showing that substituted polypeptides retain biological activity.

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The Examiner stated:

> The specification discloses an enabled utility for PTH(1-34), when the first amino acid is desamino-Ala or desamino-Gly as to be used as agonists at the PTH2 receptor. However the specific activities of the protein of SEQ ID NO:1, and assays for its activity are not disclosed.

Office Action at 4.

Applicants respectfully disagree. Specific assays are disclosed on pages 34 (section entitled: Screening for PTH-2 Receptor Agonists) and 36 (section entitled: Radioligand Binding and Signaling Assays). Results, in which the activities of the peptides are described, can be found on pages 38-56 (section entitled: Results) and in the Figures.

IV. Rejection under 35 U.S.C. § 112, Second Paragraph

In the Office Action at pages 5-6, the Examiner rejected claims 1 and 2 under 35 U.S.C. § 112, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. By the foregoing amendments, claim 1 has been cancelled, thus rendering moot the portion of this rejection that may have applied to it. Applicants respectfully traverse the rejection as it may apply to claim 2.

X_{01} is selected from desamino-Ser, desamino-Gly and desamino-Ala, and can be a part of a number of different peptides defined in claim 2. The peptides (desamino-Ser^1)hPTH(1-31)NH_2 and (desamino-Ser^1)hPTH(1-34)NH_2 are excluded from the scope of claim 2. However, (desamino-Ser^1)hPTH(1-32)NH_2 and (desamino-Ser^1)hPTH(1-33)NH_2, for example, remain within the scope of the claim. Therefore, claim 2 is not indefinite.

V. ***First Rejection under 35 U.S.C. § 102***

In the Office Action at page 6, the Examiner rejected claims 1, 2 and 5-8 under 35 U.S.C. § 102(b) as being anticipated by Toyo *et al.* (Japanese Patent 58-96052) ["Toyo"]. By the forgoing amendment, claims 1 and 7 have been cancelled, thus rendering moot the portion of this rejection that may have applied to this claim. Applicants respectfully traverse this rejection as it may be applied to the remaining claims.

Toyo discloses [desaminoSer^1]hPTH(1-34)NH_2, the peptide that is specifically excluded from the subject matter covered by claim 2. Toyo also does not disclose pharmaceutical compositions containing [desaminoSer^1]hPTH(1-34)NH_2, thus not disclosing an important element of the present invention.

Under 35 U.S.C. § 102, a claim can only be anticipated if every element in the claim is expressly or inherently disclosed in a single prior art reference. *See Kalman v. Kimberly Clark Corp.*, 713 F.2d 760, 771 (Fed. Cir. 1983), *cert. denied*, 465 U.S. 1026 (1984); *see also PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1566 (Fed. Cir. 1996) ("[t]o anticipate a claim, a reference must disclose every element of the challenged claim and enable one skilled in the art to make the anticipating subject matter."). In addition, under 35 U.S.C.§102(b), a claim can only be anticipated by a publication if the publication describes the claimed invention with sufficient detail to place the public in possession of the invention. *See In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985). Applicants respectfully assert that Toyo does not support a rejection of the invention as presently claimed under 35 U.S.C. § 102(b).

VI. Second Rejection under 35 U.S.C. § 102

In the Office Action at page 6, the Examiner rejected claims 1, 2 and 5-8 under 35 U.S.C.§102(b) as being anticipated by Rosenblatt *et al.* (U.S. Patent No. 4,423,037) ["Rosenblatt"]. By the foregoing amendments, claims 1 and 7 have been cancelled, thus rendering moot the portion of this rejection that may have applied to this claim. Applicants respectfully traverse this rejection as it may be applied to the remaining claims.

The present invention specifically claims hPTH peptides substituted at position 1. Rosenblatt discloses [Tyr^{34}]-hPTH(1-34)-NH_2 (substituted at position 34). Thus, Rosenblatt fails to disclose expressly or inherently the biologically active PTH peptides of the present invention. Hence, under *Kalman*, *PPG Industries*, and *Donohue*, Rosenblatt cannot and does not anticipate the presently claimed invention. Applicants therefore respectfully assert that Rosenblatt does not support a rejection of the invention as presently claimed under 35 U.S.C. § 102(b).

VII. Third Rejection under 35 U.S.C. § 102

In the Office Action at page 6, the Examiner rejected claims 1, 2 and 5-8 under 35 U.S.C. § 102(b) as being anticipated by Japanese Patent 59-204159 ["Daicel "]. By the foregoing amendments, claims 1 and 7 has been cancelled, thus rendering moot the portion of this rejection that may have applied to this claim. Applicants respectfully traverse this rejection as it may be applied to the remaining claims.

As discussed above, the present invention relates to PTH peptides substituted at position 1, only. Daicel discloses PTH peptides substituted at position 1, as well as at positions 8 and 18. Moreover, unlike the present invention, Daicel discloses PTH

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peptides substituted with Met(O) amino acids. Daicel, like Rosenblatt, does not disclose the biologically active PTH peptides of the present invention. Therefore, under *Kalman*, *PPG Industries*, and *Donohue*, Kramer cannot and does not anticipate the presently claimed invention. Applicants therefore respectfully assert that Daicel does not support a rejection of the invention as presently claimed under 35 U.S.C. § 102(b).

VIII. Fourth Rejection under 35 U.S.C. § 102

In the Office Action at page 7, the Examiner rejected claims 1, 2 and 5-8 under 35 U.S.C.§102(b) as being anticipated by Neer *et al.* (U.S. Patent No. 4,698,328) ["Neer"]. By the foregoing amendments, claims 1 and 7 have been cancelled, thus rendering moot the portion of this rejection that may have applied to this claim. Applicants respectfully traverse this rejection as it may be applied to the remaining claims. Neer discloses parathyroid hormone fragments but does not disclose substitution with desamino-Ser, desamino-Gly or desamino-Ala at position 1. Therefore Neer, like Daicel and Rosenblatt, fails to disclose expressly or inherently the biologically active PTH peptides of the present invention. Hence, under *Kalman*, *PPG Industries*, and *Donohue*, Neer cannot and does not anticipate the presently claimed invention. Applicants therefore respectfully assert that Neer does not support a rejection of the invention as presently claimed under 35 U.S.C. § 102(b).

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Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicant(s) therefore respectfully request(s) that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicant(s) believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Steven R. Ludwig
Attorney for Applicants
Registration No. 36,203

Date: 1/24/02

1100 New York Avenue, N.W.
Suite 600
Washington, D.C. 20005-3934
(202) 371-2600

Version with markings to show changes made

Claims 1, 7 and 9-29 are sought to be cancelled without prejudice or disclaimer.

Abstract (Once amended)

[PTH derivatives having one or more amino acid substitutions that confer PTH-1/PTH-2 receptor agonist properties comprising a biologically active peptide at least 90 % identical to a peptide consisting essentially of the formula:
X_{01}ValSerGluIleGlnLeuMetHisAsnLeuGlyLysHisLeuAsnSerMetGluArgValGluTrpLeuArgLysLysLeuGlnAspValHisAsnPhe (SEQ ID NO:1);
fragments thereof containing amino acids 1-29, 1-30, 1-31, 1-32, or 1-33;
pharmaceutically acceptable salts thereof; or
N– or C- derivatives thereof;

wherein:

X_{01} is desamino Ser, desamino Ala or desamino Gly,

provided that said peptide is not desamino Ser[1] hPTH(1-31)NH_2 or desamino Ser[1] hPTH(1-34)NH_2.]

Disclosed are novel parathyroid hormone (PTH) peptide derivatives. In particular, the invention relates to PTH derivatives having amino acid substitutions that confer PTH-1/PTH-2 receptor agonist or antagonist properties to the derivatives. Also disclosed are methods of preparing these novel derivatives, and methods of using these derivatives to treat mammalian conditions.

2. (Once amended) An isolated biologically active peptide consisting essentially of the formula:

(a) X_{01}ValSerGluIleGlnLeuMetHisAsnLeuGlyLysHisLeuAsnSerMetGluArgValGluTrpLeuArgLysLysLeuGlnAspValHisAsnPhe (SEQ ID NO:1);

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(b) fragments thereof containing amino acids 1-29, 1-30, 1-31, 1-32, or 1-33;

(c) pharmaceutically acceptable salts thereof; or

(d) N– or C- derivatives thereof;

wherein:

X_{01} is desamino Ser, desamino Ala or desamino Gly,

provided that said peptide is not (desamino-Ser^1) hPTH(1-31)NH_2 or (desamino-Ser^1) hPTH(1-34)NH_2.

3. (Once amended) The peptide of claim 2 [1] which is:

desamino-AlaValSerGluIleGlnLeuMetHisAsnLeuGlyLysHisLeuAsnSerMetGluArgVal GluTrpLeuArgLysLysLeuGlnAspValHisAsnPhe (SEQ ID NO:5).

4. (Once amended) The peptide of claim 2 [1] which is:

desamino-GlyValSerGluIleGlnLeuMetHisAsnLeuGlyLysHisLeuAsnSerMetGluArgVal GluTrpLeuArgLysLysLeuGlnAspValHisAsnPhe (SEQ ID NO:5).

5. (Once amended) The peptide of claim 2 [1] wherein the peptide is labeled with a label selected from the group consisting of: radiolabel, flourescent label, bioluminescent label, or chemiluminescent label.

8. (Once amended) A pharmaceutical composition comprising an isolated biologically active peptide consisting essentially of the formula:

(a) X_{01}ValSerGluIleGlnLeuMetHisAsnLeuGlyLysHisLeuAsnSerMet GluArgValGluTrpLeuArgLysLysLeuGlnAspValHisAsnPhe (SEQ ID NO:1);

(b) fragments thereof containing amino acids 1-29, 1-30, 1-31, 1-32, or 1-33;

(c) pharmaceutically acceptable salts thereof; or

(d) N– or C- derivatives thereof;

wherein:

X_{01} is desamino Ser, desamino Ala or desamino Gly; and a pharmaceutically acceptable carrier.